Barker
PA/04/11619


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=> dis his

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                  E "5-TETRAZOLYL"/CN 5
                  E TETRAZOLE/CN 5
L3              1 S E3
L4                STR L1
L5              0 S L4
L6              0 S L4 FUL
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L8              0 S L7
L9              2 S L7 FUL

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L4                STR
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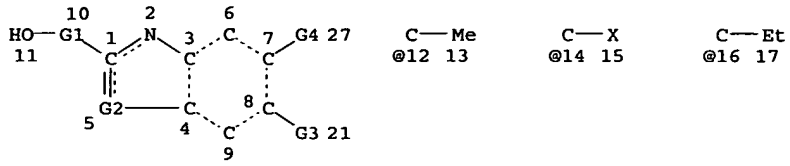

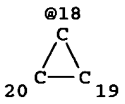

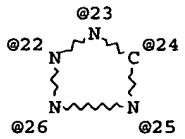


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VAR G3=ME/ET/I-PR/N-PR/18/X/O/S
VAR G4=23/24/25/22/26
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  27


Prepared by: Mary Hale @2-2507 Rem Bldg 1D86
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STEREO ATTRIBUTES: NONE
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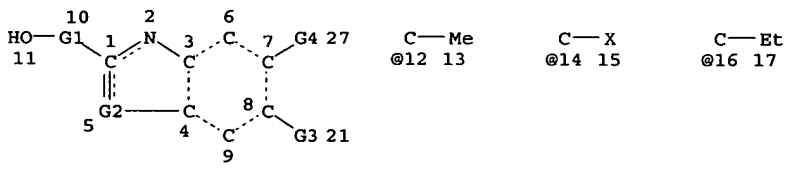
100.0% PROCESSED 5 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L7 STR



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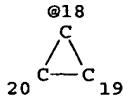

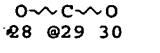

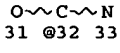

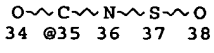

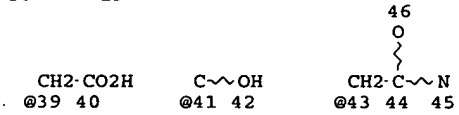

REP G1=(1-4) C
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VAR G4=CO2H/29/32/35/39/41/43
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 41

STEREO ATTRIBUTES: NONE
L9 2 SEA FILE=REGISTRY SSS FUL L7

100.0% PROCESSED 14142 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	345.00	345.21

FILE 'CAPLUS' ENTERED AT 15:57:42 ON 21 DEC 2005

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

FILE COVERS 1907 - 21 Dec 2005 VOL 143 ISS 26
FILE LAST UPDATED: 20 Dec 2005 (20051220/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

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L10 1 L9

=> d ibib abs hitstr

L10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:905878 CAPLUS
DOCUMENT NUMBER: 141:379805
TITLE: A preparation of indole derivatives, useful as PDZ-domain inhibitors
INVENTOR(S): Guy, Rodney Kiplin; Kuntz, Irwin D.; Haresco, Jose; Fujii, Naoaki; Novak, Kathleen P.; Stokoe, David; He, Biao; You, Liang; Xu, Zhidong; Jablons, David M.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092346	A2	20041028	WO 2004-US11619	20040415
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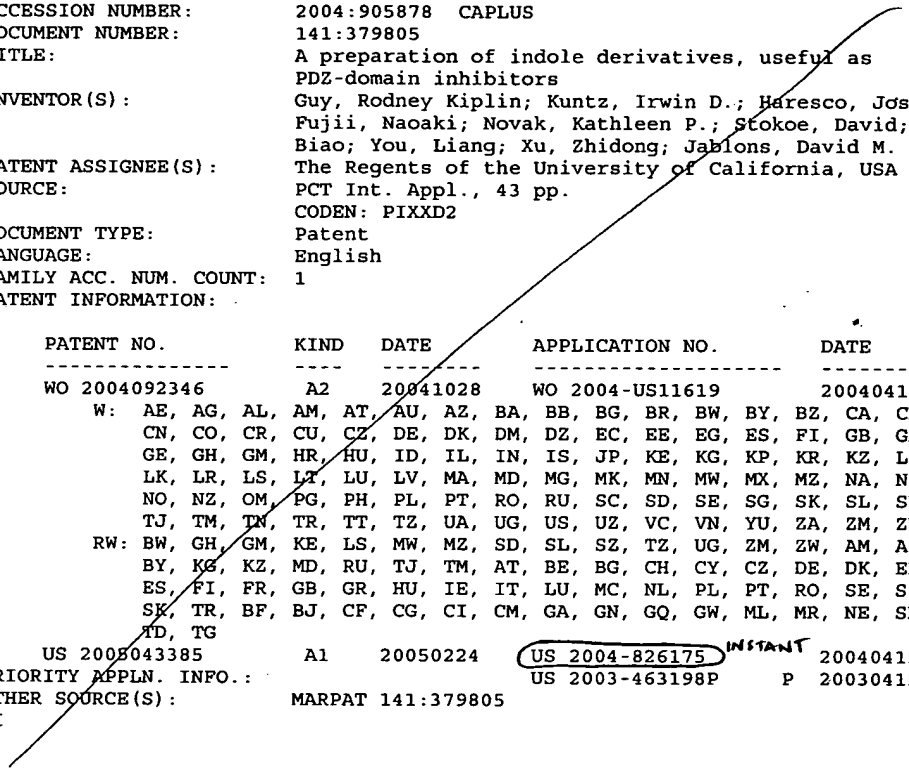
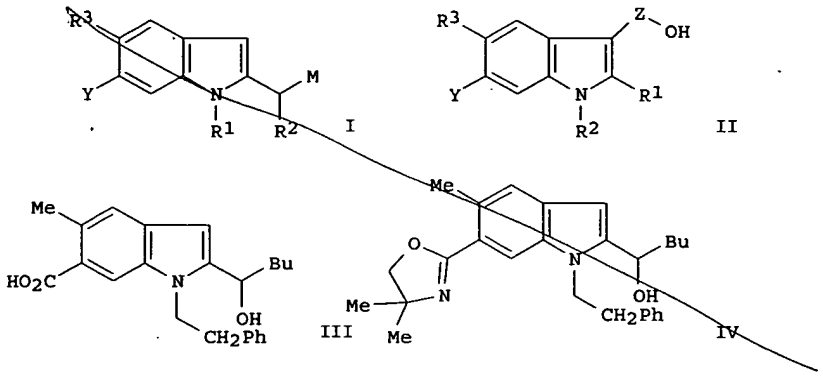
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005043385	A1	20050224	US 2004-826175 INSTANT	20040415
PRIORITY APPLN. INFO.:			US 2003-463198P P	20030415

OTHER SOURCE(S): MARPAT 141:379805
GI



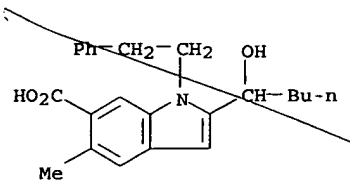
Prepared by: Mary Hale @2-2507 Rem Bldg 1D86



AB The invention relates to a preparation of novel indole derivs. of formulas I and II [wherein: R1 and R2 are independently selected from alkenyl, phenylcyclopropyl, or phenylpropenyl, etc.; R3 is H, Me, or Et; M is HO(CH2)n; X is CH, C-halogen, C(Me), or C(Et); Y is CO2H, CH2CO2H, or C(O)NH2, etc.; Z is CH2, CH(Me), CMe2, or C(O)], useful as PDZ-domain inhibitors. The invention also includes combinatorial libraries, arrays, and methods for screening and studying proteins. The compds. of the invention have produced apoptosis in certain cell lines that overexpress the Dishevelled protein (Dvl); inhibiting Wnt signaling. For instance, indolecarboxylic acid derivative III was prepared from oxazolylindole derivative IV
with a yield of 89%. Compound III was tested for apoptotic effect to represent the inhibitory effect on interaction between the PDZ domain of the Dishevelled (Dlv) protein and the Fz protein (apoptosis inhibition: 38.7% at 100 μM).

IT **782499-26-7P 782499-30-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of combinatorial library of indole derivs., useful as PDZ-domain inhibitors)

RN 782499-26-7 CAPLUS
CN 1H-Indole-6-carboxylic acid, 2-(1-hydroxypentyl)-5-methyl-1-(2-phenylethyl)- (9CI) (CA INDEX NAME)



RN 782499-30-3 CAPLUS
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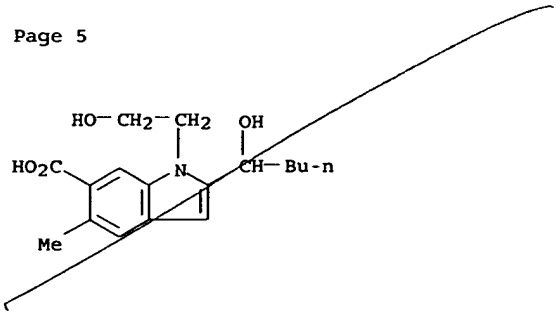


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FULL ESTIMATED COST                                    5.39     350.60

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -0.73      -0.73

FILE 'REGISTRY' ENTERED AT 15:58:03 ON 21 DEC 2005
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   20 DEC 2005  HIGHEST RN 870448-61-6
DICTIONARY FILE UPDATES:  20 DEC 2005  HIGHEST RN 870448-61-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> => d l13 que stat;fil caplus;s l13
L11             STR


Prepared by: Mary Hale @2-2507 Rem Bldg 1D86
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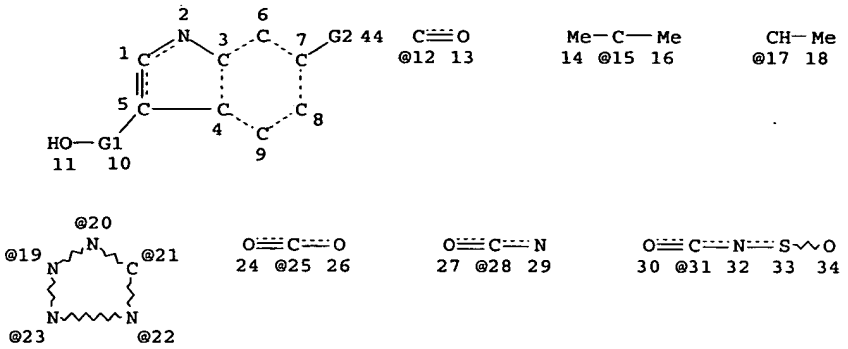

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VAR G2=CO2H/25/28/31/35/37/40/42/20/19/23/22/21
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 44

STEREO ATTRIBUTES: NONE
L13 9 SEA FILE=REGISTRY SSS FUL L11

100.0% PROCESSED 26897 ITERATIONS 9 ANSWERS
SEARCH TIME: 00.00.01

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	164.77	515.37

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-0.73

FILE 'CAPLUS' ENTERED AT 16:03:25 ON 21 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

FILE COVERS 1907 - 21 Dec 2005 VOL 143 ISS 26
FILE LAST UPDATED: 20 Dec 2005 (20051220/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

L14 8 L13

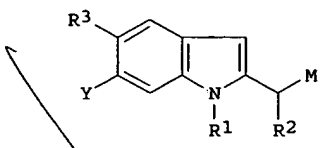
=> d 1-8 ibib abs hitstr

L14 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:905878 CAPLUS
DOCUMENT NUMBER: 141:379805
TITLE: A preparation of indole derivatives, useful as PDZ-domain inhibitors
INVENTOR(S): Guy, Rodney Kiplin; Kuntz, Irwin D.; Haresco, Jose; Fujii, Naoaki; Novak, Kathleen P.; Stokoe, David; He, Biao; You, Liang; Xu, Zhidong; Jablons, David M.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092346	A2	20041028	WO 2004-US11619	20040415
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005043385	A1	20050224	US 2004-826175 INSTANT	20040415
PRIORITY APPLN. INFO.:			US 2003-463198P P	20030415
OTHER SOURCE(S):	MARPAT 141:379805			

GI

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86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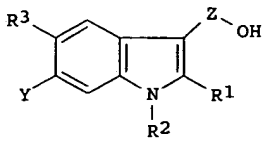
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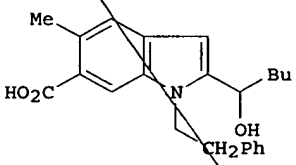
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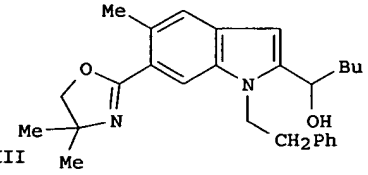
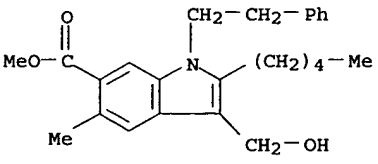

IV

AB The invention relates to a preparation of novel indole derivs. of formulas I and II [wherein: R1 and R2 are independently selected from alkenyl, phenylcyclopropyl, or phenylpropenyl, etc.; R3 is H, Me, or Et; M is HO(CH2)n; X is CH, C-halogen, C(Me), or C(Et); Y is CO2H, CH2CO2H, or C(O)NH2, etc.; Z is CH2, CH(Me), CMe2, or C(O)], useful as PDZ-domain inhibitors. The invention also includes combinatorial libraries, arrays, and methods for screening and studying proteins. The compds. of the invention have produced apoptosis in certain cell lines that overexpress the Dishevelled protein (Dvl); inhibiting Wnt signaling. For instance, indolecarboxylic acid derivative III was prepared from oxazolylindole derivative IV with a yield of 89%. Compound III was tested for apoptotic effect to represent the inhibitory effect on interaction between the PDZ domain of the Dishevelled (Dlv) protein and the Fz protein (apoptosis inhibition: 38.7% at 100 μM).

IT **782499-32-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of combinatorial library of indole derivs., useful as PDZ-domain inhibitors)

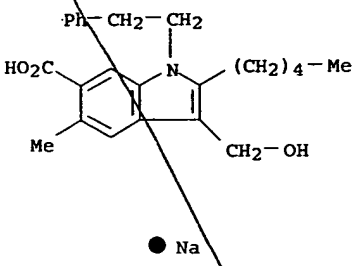
RN 782499-32-5 CAPLUS

CN 1H-Indole-6-carboxylic acid, 3-(hydroxymethyl)-5-methyl-2-pentyl-1-(2-phenylethyl)-, methyl ester (9CI) (CA INDEX NAME)



IT **618881-42-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of combinatorial library of indole derivs., useful as PDZ-domain inhibitors)

RN 618881-42-8 CAPLUS
CN 1H-Indole-6-carboxylic acid, 3-(hydroxymethyl)-5-methyl-2-pentyl-1-(2-phenylethyl)-, monosodium salt (9CI) (CA INDEX NAME)



L14 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:769887 CAPLUS
DOCUMENT NUMBER: 141:410724
TITLE: A Synthetic Approach toward the Proposed Tetracyclic Aziridinomitosene Derived from FK317
AUTHOR(S): Kim, Musong; Vedejs, Edwin
CORPORATE SOURCE: Department of Chemistry, University of Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Journal of Organic Chemistry (2004), 69(21), 7262-7265
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:410724
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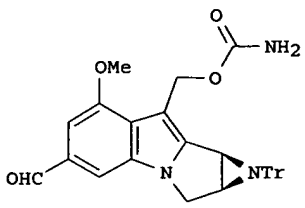

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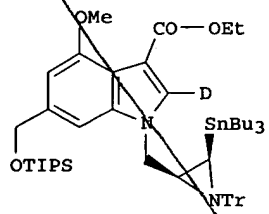

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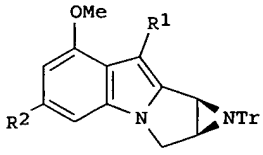
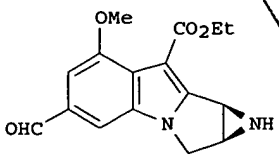


III



V

AB A synthesis of the FK317 derivative I is described using internal Michael addition Tin-lithium exchange of the deuterated stannylaziridine II

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

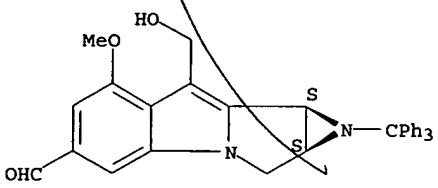
generated the key lithioaziridine intermediate, followed by cyclization and aromatization of the pyrrole ring to give III [R1 = CO2Et, R2 = CH2OTIPS (IV)]. Ester reduction from IV to III (R1 = CH2OH, R2 = CHO) was effected via temporary aldehyde protection as the silylimidazole adduct, and conversion to the carbamate I was carried out using FmocNCO and FMOC cleavage. Structure I is the N-trityl-protected derivative of the proposed intermediate from bioactivation of FK317 that is responsible for DNA crosslinking. Attempted nitrogen deprotection of I using MsOH/i-Pr3SiH resulted in replacement of the C(10) carbamate by hydride. Deprotection of the more stable III (R1 = CO2Et, R2 = CHO) gave the desired aziridine V.

IT **791807-46-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of proposed tetracyclic aziridinomitosene derived from FK317)

RN 791807-46-0 CAPLUS

CN Aziridino[2',3':3,4]pyrrolo[1,2-a]indole-5-carboxaldehyde, 1,1a,2,8b-tetrahydro-8-(hydroxymethyl)-7-methoxy-1-(triphenylmethyl)-, (1aS,8bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:606472 CAPLUS
DOCUMENT NUMBER: 141:157141
TITLE: Preparation of diazepinoindolones as CHK-1 kinase inhibitors.
INVENTOR(S): Ninkovic, Sacha; Bennett, Michael John; Rui, Yuanjin; Wang, Fen; Benedict, Suzanne Pritchett; Teng, Min
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 279 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

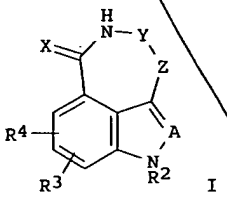
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004063198	A1	20040729	WO 2004-IB26	20040105
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ				
CA 2512683	AA	20040729	CA 2004-2512683	20040105
EP 1585749	A1	20051019	EP 2004-700145	20040105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

US 2005075499	A1	20050407	US 2004-754171	20040109
US 6967198	B2	20051122		
PRIORITY APPLN. INFO.:			US 2003-439396P	P 20030109
			WO 2004-IB26	W 20040105

OTHER SOURCE(S): MARPAT 141:157141

GI



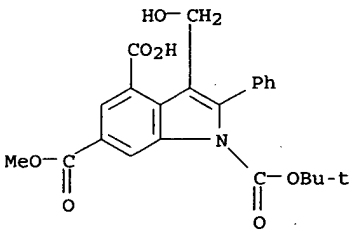
I

AB Title compds. [I; X = O , S; A = CR1, N; YZ = OCH2, N:CH; R1 = alkyl, COR5; CONR6R7, R35, R36, (substituted) alkenyl, alkynyl; R2 = H, OH, alkyl, COR8; C:SR9, C:SNR10R11, R38, R39; R3 = alkyl, COR12, CONR13R14, NR15COR16, NR17SO2R18, etc.; R4 = H, F, Br, Cl, alkyl; R5 = H, alkyl, alkoxy, R36; R6, R7 = H, alkyl, R36; R8 = alkyl, alkenyl, alkynyl, NH2, R36, R37; R9, R10, R11, R17 = H, alkyl, R36; R13, R15 = H, alkyl; R14 = H, alkyl, CH2CO2alkyl, R36; R16 = H, alkyl, alkenyl, alkynyl, NH2, R36, R37; R18 = alkyl, R36; R36 = cycloalkyl, heterocyclyl, aryl, heteroaryl; R37 = NR25R26, R27O; R25 = H, alkyl; R26 = CO2CMe3, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl; R38 = R28SOn; n = 0-2; R39 = R29R30NSOn; R28, R30 = alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl; R29 = H, alkyl], were prepared as CHK-1 inhibitors (no data). Thus, 3-formyl-5-pyridin-3-yl-1H-indole-4-carboxylic acid Me ester (preparation given), N2H4, and HOAc were heated at 80° in MeOH for 24 h to give 23% 7-pyridin-3-yl-1,5-dihydro-[1,2]diazepino[4,5,6-cd]indol-6-one.

IT **731810-39-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of diazepinoindolones as CHK-1 kinase inhibitors)

RN 731810-39-2 CAPLUS

CN 1H-Indole-1,4,6-tricarboxylic acid, 3-(hydroxymethyl)-2-phenyl-, 1-(1,1-dimethylethyl) 6-methyl ester (9CI) (CA INDEX NAME)



L14 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:727516 CAPLUS

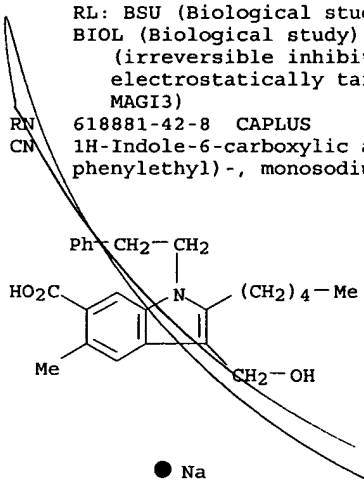
Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

DOCUMENT NUMBER: 139:347402
TITLE: A Selective Irreversible Inhibitor Targeting a PDZ Protein Interaction Domain
AUTHOR(S): Fujii, Naoaki; Haresco, Jose J.; Novak, Kathleen A. P.; Stokoe, David; Kuntz, Irwin D.; Guy, R. Kiplin
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, Laboratory for Molecular Dynamics and Design, University of California at San Francisco, San Francisco, CA, 94143-2280, USA
SOURCE: Journal of the American Chemical Society (2003), 125(40), 12074-12075
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:347402

AB Irreversible inhibitors of proteases have proven themselves useful tools for determining which proteases are active under given conditions in tissues or cells and for studying the functional role that a protease plays in physiol. processes. The application of such techniques to studying the activity and function of protein-protein interactions has been hindered by the lack of guiding principles for the mechanistic design of irreversible inhibitors which target the "active site" of a protein interaction. We report herein the first example of a mechanism-based irreversible inhibitor of a protein interaction that has been specifically targeted to one member of the PDZ family of protein interaction domains; i.e., the second PDZ domain of the membrane-associated guanylate kinase MAGI3. This inhibitor was designed using rationally directed computational evaluation to take advantage of a conserved histidine in the PDZ domain by introducing an ionizable group that will be held in close proximity to that nucleophile during binding. The novel compound exhibits all of the characteristics associated with an irreversible inhibitor of tumor suppressor PTEN interactions with MAGI3 in in vitro models. In cells, the inhibitor is shown to release PTEN from sequestration by MAGI3 and consequently upregulate the PKB signaling pathway.

IT **618881-42-8P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(irreversible inhibitor of guanylate kinase MAGI3 interaction with PTEN electrostatically targets conserved His residue in PDZ2 domain of MAGI3)

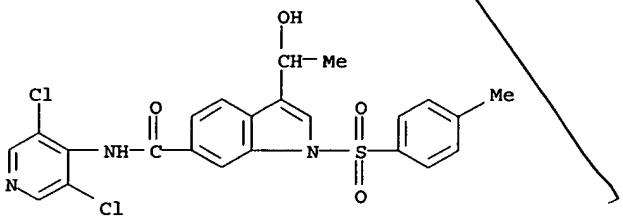
RN 618881-42-8 CAPLUS
CN 1H-Indole-6-carboxylic acid, 3-(hydroxymethyl)-5-methyl-2-pentyl-1-(2-phenylethyl)-, monosodium salt (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:515943 CAPLUS
DOCUMENT NUMBER: 129:230604
TITLE: The synthesis and biological evaluation of a novel series of indole PDE4 inhibitors I
AUTHOR(S): Hulme, Christopher; Moriarty, Kevin; Miller, Bruce; Mathew, Rose; Ramanjulu, Mercy; Cox, Paul; Souness, John; Page, Ken M.; Uhl, Joanne; Travis, Jeffrey; Huang, Fu-Chih; Labaudiniere, Richard; Djuric, Stevan W.
CORPORATE SOURCE: Rhone-Poulenc Rorer Central Research, Collegeville, PA, 19426, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1998), 8(14), 1867-1872
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This communication describes the synthesis and in vitro evaluation of a novel potent series of phosphodiesterase type (IV) (PDE-IV) inhibitors. The compds. described contain an indole moiety which replaces the "rolipram-like" 3-methoxy-4-cyclopentyloxy motif. The target compds. are derivs. of N-(3,5-dichloro-4-pyridinyl)-3-methyl-1H-indole-6-carboxamide. Several of the compds. presented possess low nanomolar IC50's for PDE-IV inhibition. In vivo activities determined from measurement of serum TNF-α levels in LPS challenged mice (mouse endotoxemia model) are also reported.
IT **201286-24-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of indole derivs. as PDE-IV inhibitors)
RN 201286-24-0 CAPLUS
CN 1H-Indole-6-carboxamide, N-(3,5-dichloro-4-pyridinyl)-3-(1-hydroxyethyl)-1-[(4-methylphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:31305 CAPLUS
DOCUMENT NUMBER: 128:102087
TITLE: Substituted azabicyclic compounds and their use as inhibitors of the production of TNF and cyclic AMP phosphodiesterase
INVENTOR(S): Cox, Paul Joseph; Bower, Shelley; Aldous, David John;

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

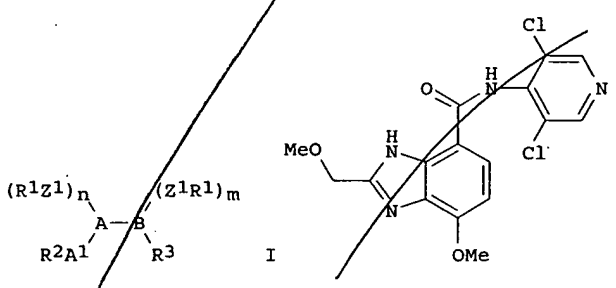
Astles, Peter Charles; McGarry, Daniel Gerard; Hulme, Christopher; et al.
PATENT ASSIGNEE(S): Regan, John Robinson, UK; Huang, Fu-Chih; Rhone-Poulenc Rorer Ltd.; Cox, Paul Joseph; Bower, Shelley; et al.
SOURCE: PCT Int. Appl., 355 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9748697	A1	19971224	WO 1997-GB1639	19970619
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2258728	AA	19971224	CA 1997-2258728	19970619
AU 9731026	A1	19980107	AU 1997-31026	19970619
ZA 9705446	A	19981221	ZA 1997-5446	19970619
EP 934307	A1	19990811	EP 1997-926148	19970619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2000509719	T2	20000802	JP 1998-502503	19970619
US 6303600	B1	20011016	US 1998-216392	19981218
US 6800645	B1	20041005	US 2000-612530	20000707
US 2002173527	A1	20021121	US 2002-109629	20020328
US 2005038069	A1	20050217	US 2004-933077	20040901

PRIORITY APPLN. INFO.:

GB 1996-12760	A	19960619
US 1996-23047P	P	19960802
WO 1997-GB1639	W	19970619
US 1998-216392	A1	19981218
US 2000-612530	A3	20000707

OTHER SOURCE(S): MARPAT 128:102087
GI



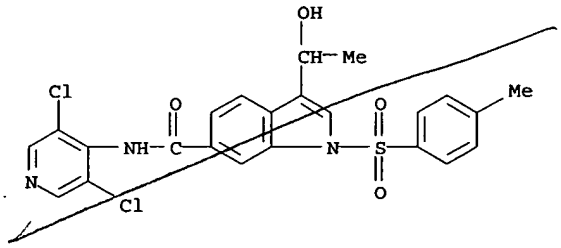
AB The invention is directed to physiol. active compds. of formula I [wherein AB = fused bicyclic ring system, of approx. 10-13 ring members, wherein A = azaheterocycle ring and B = azaheteroaryl or optionally halo-substituted benzene ring; R1 = H, (hydroxy- or halo-substituted) alkyl, and also

alkenyl, alkynyl, or CHO when Z1 = bond; R2 = H, alkenyl, alkoxy, alkyl, aryl, aryloxy, cyano, etc.; R3 = wide variety of sidechains and functional groups; A1 = bond, (un)substituted alkylene, alkenylene, alkynylene; Z1 = bond, O, S, NH; m, n = 0, 1; provided that (n+m) = 1] and their N-oxides, prodrugs, and pharmaceutically acceptable salts and solvates. I inhibit the production or physiol. effects of TNF, and inhibit cAMP phosphodiesterase (PDE IV). The invention is also directed to pharmaceutical compns. comprising I, their pharmaceutical use, and methods for their preparation For instance, 7-methoxy-2-(methoxymethyl)-3H-benzimidazole-4-carboxylic acid (preparation given) was treated with O-benzotriazol-1-yl-N,N,N',N'-bis(tetramethylene)uronium tetrafluoroborate to give the 1-benzotriazolyl ester, which was amidated with 4-amino-3,5-dichloropyridine in THF (after treatment of the latter with Na diethylaluminate) to give the title compound II. Compds. I had IC50 of 10-5 to 10-10 M against guinea pig macrophage PDE IV, with 50- to 10,000-fold selectivity for PDE IV vs. PDE I, II, III, or V. The compds. also inhibited antigen-induced bronchoconstriction in rats by up to 89% at oral doses of 10 mg/kg.

IT **201286-24-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of azabicyclic compds. as inhibitors of TNF production and PDE IV)

RN 201286-24-0 CAPLUS

CN 1H-Indole-6-carboxamide, N-(3,5-dichloro-4-pyridinyl)-3-(1-hydroxyethyl)-1-[(4-methylphenyl)sulfonyl]- (9CI) (CA INDEX NAME)



L14 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:433622 CAPLUS
DOCUMENT NUMBER: 127:103980
TITLE: DNA-DNA interstrand crosslinking by FR66979: intermediates in the activation cascade
AUTHOR(S): Paz, Manuel M.; Hopkins, Paul B.
CORPORATE SOURCE: Department of Chemistry, University of Washington, Seattle, WA, 98195, USA
SOURCE: Journal of the American Chemical Society (1997), 119(26), 5999-6005
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

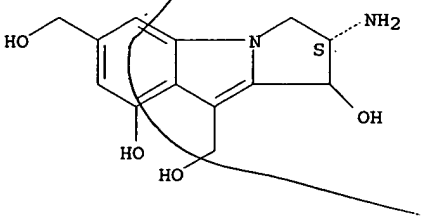
AB The antitumor antibiotics FR66979 (1), FR900482 (2), and FK973 (3) are similar in structure and biol. activity to the DNA crosslinking antitumor antibiotic mitomycin C (4). The cytotoxic effects of 1-3 have been proposed to result from sequential bioreductive cleavage of the N-O bond

and condensation of the thus-exposed amine and ketone functions to yield an indole (e.g., 9) which is structurally analogous to the mitosene nucleus of reductively activated mitomycins. We report herein evidence substantiating this proposal based upon study of the reductive activation chemical of 1 and 2 using thiols and iron(II) in the absence and presence of DNA. Prolonged exposure of reductively activated 1 to sodium borohydride afforded the dihydroindole 11, presumably through trapping of the iminium ion precursor (16). Kinetics measurements strongly implicate a relatively long-lived precursor to the iminium ion, which accumulates following iron(II)-catalyzed thiol-promoted reduction of 1, proposed herein to be one or both of the isomeric aminals 12. Under appropriate conditions, some step or steps between this intermediate and the iminium ion are shown to be rate limiting in DNA crosslinking, in production of the dihydroindole by borohydride trapping, and in the decay of the intermediate(s) competent to produce those same products. These studies clearly demonstrate the strong similarities in the cascade of reactions which follow reductive activation of FR66979 (1) [and presumably by extension FR900482 (2) and FK973 (3)] and the mitomycins.

IT **192181-25-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); PUR (Purification or recovery); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation)
(DNA-DNA interstrand crosslinking by FR66979: intermediates in the activation cascade)

RN 192181-25-2 CAPLUS
CN 1H-Pyrrolo[1,2-a]indole-6,9-dimethanol, 2-amino-2,3-dihydro-1,8-dihydroxy-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:88846 CAPLUS
DOCUMENT NUMBER: 126:199468
TITLE: Chiral Aziridinyl Radicals: An Application to the Synthesis of the Core Nucleus of FR-900482
AUTHOR(S): Ziegler, Frederick E.; Belema, Makonen
CORPORATE SOURCE: Sterling Chemistry Laboratory, Yale University, New Haven, CT, 06520-8107, USA
SOURCE: Journal of Organic Chemistry (1997), 62(4), 1083-1094
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:199468
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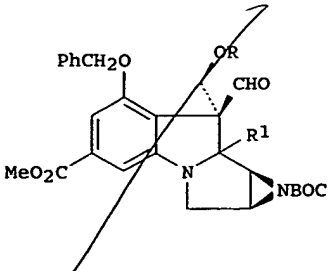
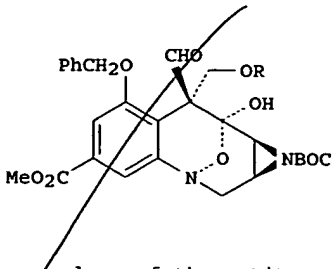


I



II

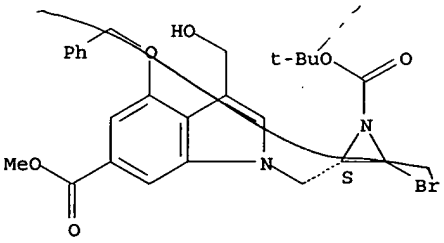
AB An asym. route to the core nucleus of the antitumor agent FR-900482 utilizes the cyclization of an aziridinyl radical into a functionalized indole nucleus. The route employs a selective Polonovski reaction and the Hootele-Dmitrienko rearrangement to install two oxygen atoms. Thus, I (R = R1 = H) (also prepared) was converted to the acetate (R = Ac) whose Polonovski reaction gave I (R = Ac, R1 = OH) selectively and the last underwent the Hootele-Dmitrienko rearrangement to give II (R = Ac) which was deacetylated and further derivatized.

IT **187682-36-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stereoselective preparation of azirinobenzazocinecarboxylates via the Hootele-Dmitrienko rearrangement of azirinopyrroloindoles)

RN 187682-36-6 CAPLUS

CN 1H-Indole-6-carboxylic acid, 1-[[3-bromo-1-[(1,1-dimethylethoxy)carbonyl]-2-aziridinyl]methyl]-3-(hydroxymethyl)-4-(phenylmethoxy)-, methyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FULL ESTIMATED COST	39.97	555.34

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Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

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DICTIONARY FILE UPDATES: 20 DEC 2005 HIGHEST RN 870448-61-6

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* The CA roles and document type information have been removed from *
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* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
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predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

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E2            1     PDY 132LEP/CN
E3            0 --> PDZ/CN
E4            1     PDZ AND LIM DOMAIN 1 (ELFIN) (HUMAN CLONE MGC:31954 IMAGE:36
                    10938)/CN
E5            1     PDZ AND LIM DOMAIN 1 (ELFIN) (HUMAN CLONE MGC:5344 IMAGE:298
                    5229)/CN

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L15          71 PDZ ?/CN

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FILE 'BIOSIS' ENTERED AT 16:04:10 ON 21 DEC 2005
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Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

FILE 'EMBASE' ENTERED AT 16:04:10 ON 21 DEC 2005

FILE 'CAPLUS' ENTERED AT 16:04:10 ON 21 DEC 2005

L16 1396 FILE MEDLINE
L17 1845 FILE BIOSIS
L18 1286 FILE EMBASE
L19 1824 FILE CAPLUS

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L21 264 FILE MEDLINE
L22 272 FILE BIOSIS
L23 242 FILE EMBASE
L24 362 FILE CAPLUS

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L26 0 FILE MEDLINE
L27 0 FILE BIOSIS
L28 0 FILE EMBASE
L29 3 FILE CAPLUS

TOTAL FOR ALL FILES
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L30 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:15963 CAPLUS
DOCUMENT NUMBER: 142:110110
TITLE: Protein logic gates made from autoregulated fusion proteins
INVENTOR(S): Lim, Wendell; Dueber, John; Yeh, Brian
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005004347	A1	20050106	US 2003-613380	20030703
WO 2005010198	A2	20050203	WO 2004-US19778	20040619

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-613380 A 20030703

AB Protein logic gates are made from autoregulated fusion proteins comprising an output **domain** and a plurality of input **domains**, wherein at least one of the input **domains** is heterologous to the output **domain**, and the input **domains** interact with each other to allosterically and external, ligand-dependently regulate the output **domain**. The output **domain** may be constitutively active, and in the absence of the ligand, the input **domains** interact to **inhibit** the output **domain**. The activity of the output **domain** is user discretionary, and may include activities that are catalytic, label-generative, metabolic-regulative, apoptotic, specific-binding, etc. Multiple input **domains** can cooperatively regulate the fusion protein in a wide variety of functionalities, including as an OR-gate, an AND-gate, and an AND-NOT-gate. The gates may be incorporated into cells and therein used to modulate cell function. **Domain** recombination was used to reprogram input control of the actin polymerization switch, N-WASP. The **PDZ domain** of a1-syntrophin and the N-WASP GBD were used as regulatory modules in the fusion protein and thus N-WASP was reengineered to respond to Cdc42 and **PDZ** ligand as opposed to Cdc42 and PIP2.

AB Protein logic gates are made from autoregulated fusion proteins comprising an output **domain** and a plurality of input **domains**, wherein at least one of the input **domains** is heterologous to the output **domain**, and the input **domains** interact with each other to allosterically and external, ligand-dependently regulate the output **domain**. The output **domain** may be constitutively active, and in the absence of the ligand, the input **domains** interact to **inhibit** the output **domain**. The activity of the output **domain** is user discretionary, and may include activities that are catalytic, label-generative, metabolic-regulative, apoptotic, specific-binding, etc. Multiple input **domains** can cooperatively regulate the fusion protein in a wide variety of functionalities, including as an OR-gate, an AND-gate, and an AND-NOT-gate. The gates may be incorporated into cells and therein used to modulate cell function. **Domain** recombination was used to reprogram input control of the actin polymerization switch, N-WASP. The **PDZ domain** of a1-syntrophin and the N-WASP GBD were used as regulatory modules in the fusion protein and thus N-WASP was reengineered to respond to Cdc42 and **PDZ** ligand as opposed to Cdc42 and PIP2.

IT Protein motifs
(**PDZ domain**, for autoinhibitory module of fusion protein; protein logic gates made from autoregulated fusion proteins)

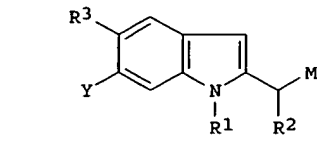
IT Allosterism
Antitumor agents
Combinatorial library
Cooperative phenomena
High throughput screening
Molecular association
Peptide library
Protein motifs
Signal transduction, biological
(protein logic gates made from autoregulated fusion proteins)

IT Proteins
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(syntrophins, a1, **PDZ domain** of, for autoinhibitory module of fusion protein; protein logic gates made from autoregulated fusion proteins)

L30 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:905878 CAPLUS
DOCUMENT NUMBER: 141:379805
TITLE: A preparation of indole derivatives, useful as **PDZ-domain inhibitors**
INVENTOR(S): Guy, Rodney Kiplin; Kuntz, Irwin D.; Haresco, Jose; Fujii, Naoaki; Novak, Kathleen P.; Stokoe, David; He, Biao; You, Liang; Xu, Zhidong; Jablons, David M.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092346	A2	20041028	WO 2004-US11619	20040415
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005043385	A1	20050224	US 2004-826175	20040415
PRIORITY APPLN. INFO.:			US 2003-463198P P	20030415

OTHER SOURCE(S): MARPAT 141:379805
GI



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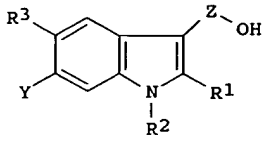

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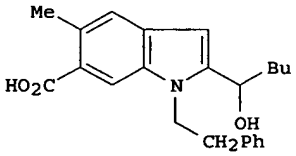
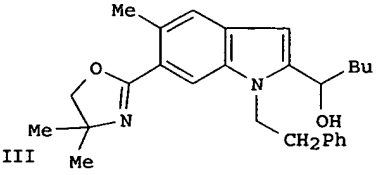


III



IV

AB The invention relates to a preparation of novel indole derivs. of formulas I and II [wherein: R1 and R2 are independently selected from alkenyl, phenylcyclopropyl, or phenylpropenyl, etc.; R3 is H, Me, or Et; M is HO(CH2)n; X is CH, C-halogen, C(Me), or C(Et); Y is CO2H, CH2CO2H, or C(O)NH2, etc.; Z is CH2, CH(Me), CMe2, or C(O)], useful as **PDZ-domain inhibitors**. The invention also includes **combinatorial libraries**, arrays, and methods for screening and studying proteins. The compds. of the invention have produced apoptosis in certain cell lines that overexpress the Dishevelled protein (Dvl); **inhibiting** Wnt signaling. For instance, indolecarboxylic acid derivative III was prepared from oxazolylindole derivative IV with a yield of 89%. Compound III was tested for apoptotic effect to represent the **inhibitory** effect on interaction between the **PDZ domain** of the Dishevelled (Dlv) protein and the Fz protein (apoptosis **inhibition**: 38.7% at 100 μM).

TI A preparation of indole derivatives, useful as **PDZ-domain inhibitors**

AB The invention relates to a preparation of novel indole derivs. of formulas I and II [wherein: R1 and R2 are independently selected from alkenyl, phenylcyclopropyl, or phenylpropenyl, etc.; R3 is H, Me, or Et; M is HO(CH2)n; X is CH, C-halogen, C(Me), or C(Et); Y is CO2H, CH2CO2H, or C(O)NH2, etc.; Z is CH2, CH(Me), CMe2, or C(O)], useful as **PDZ-domain inhibitors**. The invention also includes **combinatorial libraries**, arrays, and methods for screening and studying proteins. The compds. of the invention have produced apoptosis in certain cell lines that overexpress the Dishevelled protein (Dvl); **inhibiting** Wnt signaling. For instance, indolecarboxylic acid derivative III was prepared from oxazolylindole derivative IV with a yield of 89%. Compound III was tested for apoptotic effect to represent the **inhibitory** effect on interaction between the **PDZ domain** of the Dishevelled (Dlv) protein and the Fz protein (apoptosis **inhibition**: 38.7% at 100 μM).

ST indole prepn **PDZ domain inhibitor** antitumor

IT Protein motifs
(**PDZ domain, inhibitor**; preparation of **combinatorial library** of indole derivs., useful as **PDZ-domain inhibitors**)

IT Antitumor agents

Combinatorial library
Human
(preparation of **combinatorial library** of indole derivs., useful as **PDZ-domain inhibitors**)

IT Neoplasm
(treatment of; preparation of **combinatorial library** of indole derivs., useful as **PDZ-domain inhibitors**)

IT 18595-12-5P 618881-38-2P 618881-39-3P 618881-40-6P 618881-41-7P
686342-80-3P 782499-17-6P 782499-18-7P 782499-19-8P 782499-20-1P
782499-21-2P 782499-22-3P 782499-23-4P 782499-24-5P 782499-25-6P
782499-27-8P 782499-28-9P 782499-29-0P 782499-31-4P 782499-32-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of **combinatorial library** of indole derivs., useful as **PDZ-domain inhibitors**)

IT 618881-42-8P 782499-26-7P 782499-30-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **combinatorial library** of indole derivs., useful as **PDZ-domain inhibitors**)

IT 103-63-9, 2-Bromoethylbenzene 105-36-2, Ethyl bromoacetate 124-68-5
617-35-6, Ethyl pyruvate 628-71-7, 1-Heptyne 693-03-8,
n-Butylmagnesium bromide 1975-52-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of **combinatorial library** of indole derivs., useful as **PDZ-domain inhibitors**)

L30 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:22597 CAPLUS
DOCUMENT NUMBER: 138:85352
TITLE: T1R hetero-oligomeric taste receptors and use thereof for identification of taste compounds
INVENTOR(S): Zoller, Mark T.; Li, Xiaodong; Staszewski, Lena; O'Connell, Shawn; Zozulya, Sergey; Adler, Joan Elliott; Xu, Hong; Echeverri, Fernando
PATENT ASSIGNEE(S): Senomyx, Inc., USA
SOURCE: PCT Int. Appl., 135 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003001876	A2	20030109	WO 2002-US19970	20020626
WO 2003001876	A3	20031204		
WO 2003001876	C1	20040819		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,

	GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US	2002160424	A1	20021031	US 2001-897427	20010703
US	6955887	B2	20051018		
US	2003054448	A1	20030320	US 2002-35045	20020103
CA	2451317	AA	20030109	CA 2002-2451317	20020626
US	2003232407	A1	20031218	US 2002-179373	20020626
EP	1412750	A2	20040428	EP 2002-761016	20020626
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP	2005500318	T2	20050106	JP 2003-508132	20020626
US	2003220479	A1	20031127	US 2002-318031	20021213
US	2004175792	A1	20040909	US 2003-725103	20031202
US	2004185469	A1	20040923	US 2003-725080	20031202
US	2004209286	A1	20041021	US 2003-725276	20031202
US	2005032158	A1	20050210	US 2003-725284	20031202
US	2004175793	A1	20040909	US 2003-725489	20031203
US	2004191862	A1	20040930	US 2003-725472	20031203
US	2005084932	A1	20050421	US 2003-725418	20031203
NO	2003005761	A	20040220	NO 2003-5761	20031222
PRIORITY APPLN. INFO.:				US 2001-300434P P	20010626
				US 2001-897427 A	20010703
				US 2001-304749P P	20010713
				US 2001-310493P P	20010808
				US 2001-331771P P	20011121
				US 2001-339472P P	20011214
				US 2002-35045 A	20020103
				US 2002-372090P P	20020415
				US 2002-374143P P	20020422
				US 2002-374522P P	20020423
				US 2001-259227P P	20010103
				US 2001-284547P P	20010419
				US 2002-179373 A3	20020626
				WO 2002-US19970 W	20020626

AB The present invention relates to the discovery that the T1R receptors assemble to form functional taste receptors. Particularly, it has been discovered that co-expression of T1R1 and T1R3 results in a taste receptor that responds to umami taste stimuli, including monosodium glutamate. Also, it has been discovered that co-expression of the T1R2 and T1R3 receptors results in a taste receptor that responds to sweet taste stimuli including naturally occurring and artificial sweeteners. Also the present invention relates to the use of hetero-oligomeric taste receptors comprising T1R1/T1R3 and T1R2/T1R3 in assays to identify compds. that resp. respond to umami taste stimuli and sweet taste stimuli. Further, the invention relates to the constitutive of cell lines that stably or transiently co-express a combination of T1R1 and T1R3; or T1R2 and T1R3; under constitutive or inducible conditions. The use of these cells lines in cell-based assays to identify umami and sweet taste modulatory compds. is also provided, particularly high throughput screening assays that detect receptor activity by use of fluorometric imaging. Finally, the invention relates to the discovery that some compds., e.g., lactisole, **inhibit** both the activities of human T1R2/T1R3 and T1R1/T1R3 receptors, and accordingly the sweet and umami taste, suggesting that these receptors may be the only sweet and umami receptors. Examples of the invention show protein sequence alignments of human and rat T1R taste receptors, mRNA expression of human T1R2 and T1R3 receptors in tongue tissue, and functional data for the human T1R taste receptors.

AB The present invention relates to the discovery that the T1R receptors assemble to form functional taste receptors. Particularly, it has been discovered that co-expression of T1R1 and T1R3 results in a taste receptor

that responds to umami taste stimuli, including monosodium glutamate. Also, it has been discovered that co-expression of the T1R2 and T1R3 receptors results in a taste receptor that responds to sweet taste stimuli including naturally occurring and artificial sweeteners. Also the present invention relates to the use of hetero-oligomeric taste receptors comprising T1R1/T1R3 and T1R2/T1R3 in assays to identify compds. that resp. respond to umami taste stimuli and sweet taste stimuli. Further, the invention relates to the constitutive of cell lines that stably or transiently co-express a combination of T1R1 and T1R3; or T1R2 and T1R3; under constitutive or inducible conditions. The use of these cells lines in cell-based assays to identify umami and sweet taste modulatory compds. is also provided, particularly high throughput screening assays that detect receptor activity by use of fluorometric imaging. Finally, the invention relates to the discovery that some compds., e.g., lactisole, **inhibit** both the activities of human T1R2/T1R3 and T1R1/T1R3 receptors, and accordingly the sweet and umami taste, suggesting that these receptors may be the only sweet and umami receptors. Examples of the invention show protein sequence alignments of human and rat T1R taste receptors, mRNA expression of human T1R2 and T1R3 receptors in tongue tissue, and functional data for the human T1R taste receptors.

IT Protein motifs
(**PDZ domain**, interacting peptide, fusion products; T1R hetero-oligomeric taste receptors and use thereof for identification of taste compds.)

IT Amphibia
Aves
Bos taurus
Canis familiaris
Combinatorial library
Drug screening
Drugs
Felis catus
Fish
Food additives
Human
Mammalia
Molecular association
Molecular cloning
Mus
Ovis aries
Peptide library
Rattus
Reptilia
Sus scrofa domestica
Sweetening agents
Sweetness
Transformation, genetic
Viral vectors
(T1R hetero-oligomeric taste receptors and use thereof for identification of taste compds.)

IT 138464-10-5, Gurmarin
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(T1R2/T1R3 receptor **inhibitor**; T1R hetero-oligomeric taste receptors and use thereof for identification of taste compds.)

IT 150436-68-3, Lactisole
RL: BUU (Biological use, unclassified); CUS (Combinatorial use); BIOL (Biological study); CMBI (Combinatorial study); USES (Uses)
(**inhibitor** of T1R receptors; T1R hetero-oligomeric taste receptors and use thereof for identification of taste compds.)

```
=> s l20 and screen?
L31         162 FILE MEDLINE
L32         239 FILE BIOSIS
L33         152 FILE EMBASE
L34         284 FILE CAPLUS

TOTAL FOR ALL FILES
L35         837 L20 AND SCREEN?

=> s small molecule and (l35 or l25)
L36           0 FILE MEDLINE
L37           1 FILE BIOSIS
L38           0 FILE EMBASE
L39           6 FILE CAPLUS

TOTAL FOR ALL FILES
L40           7 SMALL MOLECULE AND (L35 OR L25)

=> dup rem l40
PROCESSING COMPLETED FOR L40
L41           7 DUP REM L40 (0 DUPLICATES REMOVED)

=> d 1-7 ibib abs hit

L41  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2005:1130664  CAPLUS
DOCUMENT NUMBER:         143:410916
TITLE:                   Peptides derived from the C-terminus of voltage-gated
                         calcium channel CaV2.2 for inhibiting pain
INVENTOR(S):             Garry, Mary; Bezprozvanny, Ilya
PATENT ASSIGNEE(S):      Board of Regents, the University of Texas System, USA
SOURCE:                  PCT Int. Appl., 106 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
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     WO 2005097828         A2    20051020    WO 2005-US10642        20050331
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,
             SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
     US 2005267036         A1    20051201    US 2005-96281          20050331
PRIORITY APPLN. INFO.:                       US 2004-558383P     P  20040401
AB   The present invention relates to peptides of CaV2.2 and their use in the
     treatment of pain.  The sequence of the peptides is derived from the
     C-terminus of CaV2.2 and is believed to inhibit the interaction
     of CaV2.2 with Mint1-PDZ1.  The invention is related to use of this
```

peptide to treat pain and to use of this peptide in binding reaction with Mint-PDZ to screen for small mols. that can inhibit pain.

TI Peptides derived from the C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain

AB The present invention relates to peptides of CaV2.2 and their use in the treatment of pain. The sequence of the peptides is derived from the C-terminus of CaV2.2 and is believed to inhibit the interaction of CaV2.2 with Mint1-PDZ1. The invention is related to use of this peptide to treat pain and to use of this peptide in binding reaction with Mint-PDZ to screen for small mols. that can inhibit pain.

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(APBA2 (amyloid β A4 precursor protein-binding family A member 2); peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Peptides, biological studies
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(CaV2.2; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Protein motifs
(Mint1-PDZ1; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PDZ domain-containing; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(R9, TAT sequence; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(immediate early, promoter from; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Tumor antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(large T, promoter from; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Drug delivery systems
(liposomes; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Nerve, disease
Pain
(neuralgia, treatment of; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Anti-inflammatory agents
(nonsteroidal; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Inflammation
Neoplasm
(pain, treatment of; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for inhibiting pain)

IT Adenoviral vectors
Analgesics
Animal
Bos taurus

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

Canis familiaris
Drug design
Drug **screening**
Drug targets
Equus caballus
Felis catus
Gene therapy
Genetic vectors
Human
Molecular cloning
Mus musculus
Oryctolagus cuniculus
Protein sequences
Rattus
Retroviral vectors
Viral vectors
(peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT Opioids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT Steroids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(polyadenylation signal; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT Cytomegalovirus
Rous sarcoma virus
Simian virus 40
(promoter from; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT Pain
(treatment of; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT Adeno-associated virus
Herpesviridae
Polyomavirus
Vaccinia virus
(vector; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vehicle; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT Calcium channel
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(voltage-gated, CaV2.2; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT 867144-13-6P 867144-14-7P 867144-15-8P 867144-16-9P 867144-17-0P

867144-18-1P 867144-19-2P 867144-20-5P 867144-21-6P
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pain **inhibiting** peptide sequence; peptides derived from C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT 867227-40-5 867227-42-7
RL: PRP (Properties)
(unclaimed nucleotide sequence; peptides derived from the C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

IT 867227-41-6 867227-43-8
RL: PRP (Properties)
(unclaimed protein sequence; peptides derived from the C-terminus of voltage-gated calcium channel CaV2.2 for **inhibiting** pain)

L41 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:1123740 CAPLUS
DOCUMENT NUMBER: 143:416224
TITLE: Agents disrupting the interaction between postsynaptic density protein 95 and neuronal nitric oxide synthase for use as analgesics
INVENTOR(S): Janosky, Christine Loh; Lai, Yvonne Yee-Wen
PATENT ASSIGNEE(S): Icos Corporation, USA
SOURCE: PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005097090	A2	20051020	WO 2005-US11774	20050404

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-559491P P 20040405

AB Agents capable of disrupting an interaction between neuronal nitrous oxide synthase (nNOS) and postsynaptic d. protein 95 (PSD95) and related proteins are described for use as analgesics. The agents include **small mol.** compds., natural product exts., peptides, and fusion proteins. Treatable conditions include pain, opiate tolerance, ischemic brain damage, neurol. disorders, neurodegenerative disorders, Parkinson's disease, epilepsy, seizures, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and psychiatric disorders. The interaction between nNOS and PSD95 was shown to depend on **PDZ domains.** This was adapted to a high throughput **screen** of a chemical library of 158752 members for effectors of the interaction using biotinylated PSD95 with europium-labeled streptavidin s the reporter in a time-delayed fluorescence assay. Candidate compds. were then tested for their effectiveness in **inhibiting** NMDA-dependent nitric

oxide synthesis and toxicity in rat hippocampal cells in vitro. Candidates that passed this test were **screened** for effectiveness in several rat pain models and one compound was found to be effective in most of the pain models without affecting other NMDA-dependent processes.

AB Agents capable of disrupting an interaction between neuronal nitrous oxide synthase (nNOS) and postsynaptic d. protein 95 (PSD95) and related proteins are described for use as analgesics. The agents include **small mol.** compds., natural product exts., peptides, and fusion proteins. Treatable conditions include pain, opiate tolerance, ischemic brain damage, neurol. disorders, neurodegenerative disorders, Parkinson's disease, epilepsy, seizures, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and psychiatric disorders. The interaction between nNOS and PSD95 was shown to depend on **PDZ domains.** This was adapted to a high throughput **screen** of a chemical library of 158752 members for effectors of the interaction using biotinylated PSD95 with europium-labeled streptavidin s the reporter in a time-delayed fluorescence assay. Candidate compds. were then tested for their effectiveness in **inhibiting** NMDA-dependent nitric oxide synthesis and toxicity in rat hippocampal cells in vitro. Candidates that passed this test were **screened** for effectiveness in several rat pain models and one compound was found to be effective in most of the pain models without affecting other NMDA-dependent processes.

ST nitric oxide synthase PSD95 interaction **inhibition** analgesic

IT Protein motifs
(**PDZ domain**, in interactions of neuronal nitric oxide synthase; agents disrupting interaction between PSD95 and neuronal nitric oxide synthase for use as analgesics)

IT Actinomyces
(analgesic **inhibitor** of PSD95/nNOS interactions from; agents disrupting interaction between PSD95 and neuronal nitric oxide synthase for use as analgesics)

IT Transcription factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tat, fusion products with nNOS, as analgesic **inhibitor** of PSD95/nNOS interactions from; agents disrupting interaction between PSD95 and neuronal nitric oxide synthase for use as analgesics)

IT 6640-28-4 30057-19-3 91719-08-3 98068-68-9 100726-66-7 104226-33-7 104226-36-0 105541-09-1 126839-84-7 388598-13-8 416863-01-9 416867-14-6 416870-24-1 866927-10-8 866927-11-9 866927-12-0 866927-13-1 866927-14-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as analgesic **inhibitor** of PSD95/nNOS interactions; agents disrupting interaction between PSD95 and neuronal nitric oxide synthase for use as analgesics)

IT 52-26-6, Morphine hydrochloride 57-27-2, Morphine, biological studies 57-42-1, Meperidine 64-31-3, Morphine sulfate 71-68-1, Hydromorphone hydrochloride 76-99-3 124-90-3, Oxycodone hydrochloride 125-69-9, Dextromethorphan hydrobromide 125-72-4, Levorphanol tartrate 143-71-5, Hydrocodone bitartrate 302-31-8, Morphine tartrate 357-07-3, Oxymorphone hydrochloride 437-38-7, Fentanyl 466-99-9, Hydromorphone 469-62-5, Propoxyphene 561-27-3, Diacetylmorphine 1420-53-7, Codeine sulfate 1502-95-0, Diacetylmorphine hydrochloride 56030-54-7 71195-58-9, Alfentanyl 132875-61-7, Remifentanil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pain management with **inhibitor** of PSD95/nNOS interactions and; agents disrupting interaction between PSD95 and neuronal nitric oxide synthase for use as analgesics)

L41 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:1184816 CAPLUS

TITLE: Identification of a Specific **Inhibitor** of the Dishevelled **PDZ Domain**
AUTHOR(S): Shan, Jufang; Shi, De-Li; Wang, Junmei; Zheng, Jie
CORPORATE SOURCE: Department of Structural Biology, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Biochemistry (2005), 44(47), 15495-15503
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Wnt signaling pathways are involved in embryo development as well as in tumorigenesis. Dishevelled (Dvl) transduces Wnt signals from the receptor Frizzled (Fz) to downstream components in canonical and noncanonical Wnt signaling pathways. The Dvl **PDZ domain** is thought to play an essential role in **both** pathways, and we recently demonstrated that the Dvl **PDZ domain** binds directly to Fz receptors. In this study, using structure-based virtual ligand **screening**, we identified an organic mol. (NSC668036) from the National Cancer Institute **small-mol.** library that can bind to the Dvl **PDZ domain.** We then used mol. dynamics simulation to analyze the binding between the **PDZ domain** and NSC668036 in detail. In addition, we showed that, in Xenopus, as expected, NSC668036 **inhibited** the signaling induced by Wnt3A. This compound provides a basis for rational design of high-affinity **inhibitors** of the **PDZ domain,** which can block Wnt signaling by interrupting the Fz-Dvl interaction.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Identification of a Specific **Inhibitor** of the Dishevelled **PDZ Domain**

AB The Wnt signaling pathways are involved in embryo development as well as in tumorigenesis. Dishevelled (Dvl) transduces Wnt signals from the receptor Frizzled (Fz) to downstream components in canonical and noncanonical Wnt signaling pathways. The Dvl **PDZ domain** is thought to play an essential role in both pathways, and we recently demonstrated that the Dvl **PDZ domain** binds directly to Fz receptors. In this study, using structure-based virtual ligand **screening**, we identified an organic mol. (NSC668036) from the National Cancer Institute **small-mol.** library that can bind to the Dvl **PDZ domain.** We then used mol. dynamics simulation to analyze the binding between the **PDZ domain** and NSC668036 in detail. In addition, we showed that, in Xenopus, as expected, NSC668036 **inhibited** the signaling induced by Wnt3A. This compound provides a basis for rational design of high-affinity **inhibitors** of the **PDZ domain,** which can block Wnt signaling by interrupting the Fz-Dvl interaction.

ST NSC668036 **inhibitor** dishevelled **PDZ domain** Wnt signaling

IT INDEXING IN PROGRESS
IT INDEXING IN PROGRESS
IT Proteins
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(DVL (dishevelled); identification of a specific **inhibitor** of dishevelled **PDZ domain**)
IT Protein motifs
(**PDZ domain**; identification of a specific **inhibitor** of dishevelled **PDZ domain**)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

(Wnt; identification of a specific **inhibitor** of dishevelled **PDZ domain**)
IT Molecular association
Signal transduction, biological
Xenopus
(identification of a specific **inhibitor** of dishevelled **PDZ domain**)
IT Simulation and Modeling
(mol. dynamics; identification of a specific **inhibitor** of dishevelled **PDZ domain**)
IT Conformation
(protein; identification of a specific **inhibitor** of dishevelled **PDZ domain**)

L41 ANSWER 4 OF 7 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:124384 BIOSIS
DOCUMENT NUMBER: PREV200400127300
TITLE: Virtual ligand **screening** of small **inhibitors** of the Dvl **PDZ domain**
AUTHOR(S): Shan, Jufang [Reprint Author]; Zheng, Jie [Reprint Author]
CORPORATE SOURCE: Department of Structural Biology, St. Jude Children's Research Hospital, Memphis, TN, USA
SOURCE: Biophysical Journal, (January 2004) Vol. 86, No. 1, pp. 307a. print.
Meeting Info.: 48th Annual Meeting of the Biophysical Society. Baltimore, MD, USA. February 14-18, 2004.
Biophysical Society.
ISSN: 0006-3495 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004

AB Dishevelled (Dvl) is a key component of Wnt signaling pathways, which play an important role in embryo development as well as tumor genesis. Dvl transduce Wnt signals from Frizzled (Fz) to stabilize beta-catenin in canonical Wnt signaling pathways and to activate c-Jun N-terminal kinase (JNK) in non-canonical Wnt signaling pathways. The Dvl **PDZ domain** is suggested to be involved in both pathways. In a recent report, we demonstrated that it directly binds to the Fz receptors, and proposed such interaction plays an essential role in the Wnt signaling. In this study, using NMR-assisted virtual ligand **screening**, we conducted a search to define **small molecules** that can bind to the Dvl **PDZ domain** and block the interaction between Fz and Dvl. In detail, we first designed queries to search potential **inhibitors** in large databases with Sybyl(R) module Unity(R) based on the structure of this **domain.** We then docked the resulting compounds using Sybyl(R) module FlexXTM. Best conformations are extracted and scored by Sybyl(R) module CscoreTM. In addition, we also docked these compounds using ICM-VLS, a different software package, to obtain more docking information. High scored compounds were obtained and tested by biophysical methods, mainly NMR spectroscopy. The positive hits were further evaluated by mapping the binding sites on the surface of the **PDZ domain** using chemical shift perturbation experiments and determining the binding affinities using fluorescence spectroscopy. These identified reagents should block the Wnt signaling by interrupting the Fz-Dvl interaction, and can serve as a powerful tool to dissect the molecular mechanism underling the Wnt pathways. Furthermore, our study may also be helpful in formulating rational approaches to the

development of novel pharmaceutical agents that can interfere with specific Wnt signal events that contribute to cancer and other human diseases.

TI Virtual ligand **screening** of small **inhibitors** of the Dvl **PDZ domain.**

AB Dishevelled (Dvl) is a key component of Wnt signaling pathways, which play an important role in embryo development as well as tumor genesis. Dvl transduce Wnt signals from Frizzled (Fz) to stabilize beta-catenin in canonical Wnt signaling pathways and to activate c-Jun N-terminal kinase (JNK) in non-canonical Wnt signaling pathways. The Dvl **PDZ domain** is suggested to be involved in both pathways. In a recent report, we demonstrated that it directly binds to the Fz receptors, and proposed such interaction plays an essential role in the Wnt signaling. In this study, using NMR-assisted virtual ligand **screening**, we conducted a search to define **small molecules** that can bind to the Dvl **PDZ domain** and block the interaction between Fz and Dvl. In detail, we first designed queries to search potential **inhibitors** in large databases with Sybyl(R) module Unity(R) based on the structure of this **domain.** We then docked the resulting compounds using Sybyl(R) module FlexXTM. Best conformations are extracted and scored by Sybyl(R) module CscoreTM. In addition, we also docked these compounds using ICM-VLS, a different software package, to obtain more docking information. High scored compounds were obtained and tested by biophysical methods, mainly NMR spectroscopy. The positive hits were further evaluated by mapping the binding sites on the surface of the **PDZ domain** using chemical shift perturbation experiments and determining the binding affinities using fluorescence spectroscopy. These identified reagents should block the Wnt signaling by interrupting the Fz-Dvl interaction, and can serve as a powerful tool to dissect the molecular mechanism underling the Wnt pathways. Furthermore, our study may also be helpful in formulating rational approaches to the development of novel pharmaceutical agents that can interfere with specific Wnt signal events that contribute to cancer and other human diseases.

IT Major Concepts
Biochemistry and Molecular Biophysics; Chemical Coordination and Homeostasis; Computer Applications (Computational Biology); Pharmacology

IT Chemicals & Biochemicals
Dvl **PDZ domains**: small **inhibitors**; Fz receptors; ligands; proteins; **small molecules**: pharmacological properties

IT Methods & Equipment
ICM-VLS software package: computer software; NMR: laboratory techniques, spectrum analysis techniques; fluorescence spectroscopy: laboratory techniques, spectrum analysis techniques; virtual ligand **screening**: laboratory techniques

IT Miscellaneous Descriptors
Wnt signaling pathways: functions; chemical shift perturbation experiments: results; drug design: structure-based; drug development; human pathologies: treatment methods; methodology; molecular interactions

L41 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:813117 CAPLUS
DOCUMENT NUMBER: 134:113493
TITLE: Identification of guanine nucleotide exchange factors (GEFs) for the Rap1 GTPase. Regulation of MR-GEF by M-Ras-GTP interaction
AUTHOR(S): Rebhun, John F.; Castro, Ariel F.; Quilliam, Lawrence

A.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology and Walther Oncology Center, Indiana University School of Medicine, Indianapolis, IN, 46202, USA
SOURCE: Journal of Biological Chemistry (2000), 275(45), 34901-34908
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although the Ras subfamily of GTPases consists of .apprx.20 members, only a limited number of guanine nucleotide exchange factors (GEFs) that couple extracellular stimuli to Ras protein activation have been identified. Furthermore, no novel downstream effectors have been identified for the M-Ras/R-Ras3 GTPase. Here we report the identification and characterization of three Ras family GEFs that are most abundantly expressed in brain. Two of these GEFs, MR-GEF (M-Ras-regulated GEF, KIAA0277) and **PDZ**-GEF (KIAA0313) bound specifically to nucleotide-free Rap1 and Rap1/Rap2, resp. Both proteins functioned as Rap1 GEFs in vivo. A third GEF, GRP3 (KIAA0846), activated both Ras and Rap1 and shared significant sequence homol. with the calcium- and diacylglycerol-activated GEFs, GRP1 and GRP2. Similarly to previously identified Rap GEFs, C3G and Smg GDS, each of the newly identified exchange factors promoted the activation of Elk-1 in the LNCaP prostate tumor cell line where B-Raf can couple Rap1 to the extracellular receptor-activated kinase cascade. MR-GEF and **PDZ**-GEF both contain a region immediately N-terminal to their catalytic **domains** that share sequence homol. with Ras-associating or Ral-GDS/AF6 homol. (RA) **domains**. By searching for in vitro interaction with Ras-GTP proteins, **PDZ**-GEF specifically bound to Rap1A- and Rap2B-GTP, whereas MR-GEF bound to M-Ras-GTP. C-terminally truncated MR-GEF, lacking the GEF catalytic **domain**, retained its ability to bind M-Ras-GTP, suggesting that the RA **domain** is important for this interaction. Co-immunopptn. studies confirmed the interaction of M-Ras-GTP with MR-GEF in vivo. In addition, a constitutively active M-Ras(71L) mutant **inhibited** the ability of MR-GEF to promote Rap1A activation in a dose-dependent manner. These data suggest that M-Ras may **inhibit** Rap1 in order to elicit its biol. effects.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Although the Ras subfamily of GTPases consists of .apprx.20 members, only a limited number of guanine nucleotide exchange factors (GEFs) that couple extracellular stimuli to Ras protein activation have been identified. Furthermore, no novel downstream effectors have been identified for the M-Ras/R-Ras3 GTPase. Here we report the identification and characterization of three Ras family GEFs that are most abundantly expressed in brain. Two of these GEFs, MR-GEF (M-Ras-regulated GEF, KIAA0277) and **PDZ**-GEF (KIAA0313) bound specifically to nucleotide-free Rap1 and Rap1/Rap2, resp. Both proteins functioned as Rap1 GEFs in vivo. A third GEF, GRP3 (KIAA0846), activated both Ras and Rap1 and shared significant sequence homol. with the calcium- and diacylglycerol-activated GEFs, GRP1 and GRP2. Similarly to previously identified Rap GEFs, C3G and Smg GDS, each of the newly identified exchange factors promoted the activation of Elk-1 in the LNCaP prostate tumor cell line where B-Raf can couple Rap1 to the extracellular receptor-activated kinase cascade. MR-GEF and **PDZ**-GEF both contain a region immediately N-terminal to their catalytic **domains** that share sequence homol. with Ras-associating or Ral-GDS/AF6 homol. (RA) **domains**. By searching for in vitro interaction with Ras-GTP

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IT G proteins (guanine nucleotide-binding proteins)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(smg-21 (**small-mol.**-weight, 21,000-mol.-weight); identification of guanine nucleotide exchange factors (GEFs) for the Rap1 GTPase in relation to regulation of MR-GEF by M-Ras-GTP interaction)

L41 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:42581 CAPLUS
DOCUMENT NUMBER: 132:177208
TITLE: PDZ-GEF1, a guanine nucleotide exchange factor specific for Rap1 and Rap2
AUTHOR(S): De Rooij, Johan; Boenink, Nienke M.; Van Triest, Miranda; Cool, Robbert H.; Wittinghofer, Alfred; Bos, Johannes L.
CORPORATE SOURCE: The Laboratory for Physiological Chemistry and Center for Biomedical Genetics, Utrecht University, Utrecht, 3584 CG, Neth.
SOURCE: Journal of Biological Chemistry (1999), 274(53), 38125-38130
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The small GTPase Rap1 has been implicated in a variety of cellular processes including the control of cell morphol., proliferation, and differentiation. Stimulation of a large variety of cell surface receptors results in the rapid activation of Rap1, i.e. an increase in the GTP-bound form. This activation is mediated by second messengers like calcium, cAMP, and diacylglycerol, but addnl. pathways may exist as well. Here we describe a ubiquitously expressed guanine nucleotide exchange factor of 200 kDa that activates Rap1 both in vivo and in vitro. This exchange factor has two putative regulatory **domains**: a **domain** with an amino acid sequence related to cAMP-binding **domains** and a **PDZ domain**. Therefore, we named it **PDZ**-GEF1. **PDZ**-GEFs are closely related to Epacs, Rap-specific exchange factors with a genuine cAMP binding site, that are directly regulated by cAMP. The **domain** related to cAMP-binding **domains**, like the cAMP binding site in Epac, serves as a neg. regulatory **domain**. However, **PDZ**-GEF1 does not interact with cAMP or cGMP. Interestingly, **PDZ**-GEF1 also activates Rap2, a close relative of Rap1. This is the first example of an exchange factor acting on Rap2. We conclude that **PDZ**-GEF1 is a guanine nucleotide exchange factor, specific for Rap1 and Rap2, that is controlled by a neg. regulatory **domain**.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The small GTPase Rap1 has been implicated in a variety of cellular processes including the control of cell morphol., proliferation, and

differentiation. Stimulation of a large variety of cell surface receptors results in the rapid activation of Rap1, i.e. an increase in the GTP-bound form. This activation is mediated by second messengers like calcium, cAMP, and diacylglycerol, but addnl. pathways may exist as well. Here we describe a ubiquitously expressed guanine nucleotide exchange factor of 200 kDa that activates Rap1 both in vivo and in vitro. This exchange factor has two putative regulatory **domains**: a **domain** with an amino acid sequence related to cAMP-binding **domains** and a **PDZ domain**. Therefore, we named it **PDZ**-GEF1. **PDZ**-GEFs are closely related to Epacs, Rap-specific exchange factors with a genuine cAMP binding site, that are directly regulated by cAMP. The **domain** related to cAMP-binding **domains**, like the cAMP binding site in Epac, serves as a neg. regulatory **domain**. However, **PDZ**-GEF1 does not interact with cAMP or cGMP. Interestingly, **PDZ**-GEF1 also activates Rap2, a close relative of Rap1. This is the first example of an exchange factor acting on Rap2. We conclude that **PDZ**-GEF1 is a guanine nucleotide exchange factor, specific for Rap1 and Rap2, that is controlled by a neg. regulatory **domain**.

IT Guanine nucleotide exchange factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**PDZ**-GEF1; novel guanine nucleotide exchange factor **PDZ**-GEF1 activates Rap1 and Rap2 and is controlled by neg. regulatory **domain**)

IT Protein motifs
(RCBD (related to cAMP-binding **domains**); RCBD functions as **inhibitory domain** in **PDZ**-GEF1; novel guanine nucleotide exchange factor **PDZ**-GEF1 activates Rap1 and Rap2 and is controlled by neg. regulatory **domain**)

IT G proteins (guanine nucleotide-binding proteins)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene rap2; novel guanine nucleotide exchange factor **PDZ**-GEF1 activates Rap1 and Rap2 and is controlled by neg. regulatory **domain**)

IT Protein sequences
(homol., homol. of catalytic **domains** of **PDZ**-GEF1 and GEFs for Ras-like GTPases; novel guanine nucleotide exchange factor **PDZ**-GEF1 activates Rap1 and Rap2 and is controlled by neg. regulatory **domain**)

IT G proteins (guanine nucleotide-binding proteins)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(smg-21 (**small-mol.**-weight, 21,000-mol.-weight); novel guanine nucleotide exchange factor **PDZ**-GEF1 activates Rap1 and Rap2 and is controlled by neg. regulatory **domain**)

L41 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:42542 CAPLUS
DOCUMENT NUMBER: 132:177207
TITLE: RA-GEF, a novel Rap1A guanine nucleotide exchange factor containing a Ras/Rap1A-associating domain, is conserved between nematode and humans
AUTHOR(S): Liao, Yanhong; Kariya, Ken-Ichi; Hu, Chang-Deng; Shibatohge, Mitsushige; Goshima, Masahiro; Okada, Tomoyo; Watari, Yasuhiro; Gao, Xianlong; Jin, Tai-Guang; Yamawaki-Kataoka, Yuriko; Kataoka, Tohru
CORPORATE SOURCE: The Department of Physiology II, Kobe University School of Medicine, Kobe, 650-0017, Japan

SOURCE: Journal of Biological Chemistry (1999), 274(53), 37815-37820
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A yeast two-hybrid **screening** for Ras-binding proteins in nematode Caenorhabditis elegans has identified a guanine nucleotide exchange factor (GEF) containing a Ras/Rap1A-associating (RA) **domain**, termed Ce-RA-GEF. Both Ce-RA-GEF and its human counterpart Hs-RA-GEF possessed a PSD-95/DlgA/ZO-1 (**PDZ**) **domain** and a Ras exchanger motif (REM) **domain** in addition to the RA and GEF **domains**. They also contained a region homologous to a cyclic nucleotide monophosphate-binding **domain**, which turned out to be incapable of binding cAMP or cGMP. Although the REM and GEF **domains** are conserved with other GEFs acting on Ras family small GTP-binding proteins, the RA and **PDZ domains** are unseen in any of them. Hs-RA-GEF exhibited not only a GTP-dependent binding activity to Rap1A at its RA **domain** but also an activity to stimulate GDP/GTP exchange of Rap1A both in vitro and in vivo at the segment containing its REM and GEF **domains**. However, it did not exhibit any binding or GEF activity toward Ras. On the other hand, Ce-RA-GEF associated with and stimulated GDP/GTP exchange of both Ras and Rap1A. These results indicate that Ce-RA-GEF and Hs-RA-GEF define a novel class of Rap1A GEF mols., which are conserved through evolution.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A yeast two-hybrid **screening** for Ras-binding proteins in nematode Caenorhabditis elegans has identified a guanine nucleotide exchange factor (GEF) containing a Ras/Rap1A-associating (RA) **domain**, termed Ce-RA-GEF. Both Ce-RA-GEF and its human counterpart Hs-RA-GEF possessed a PSD-95/DlgA/ZO-1 (**PDZ**) **domain** and a Ras exchanger motif (REM) **domain** in addition to the RA and GEF **domains**. They also contained a region homologous to a cyclic nucleotide monophosphate-binding **domain**, which turned out to be incapable of binding cAMP or cGMP. Although the REM and GEF **domains** are conserved with other GEFs acting on Ras family small GTP-binding proteins, the RA and **PDZ domains** are unseen in any of them. Hs-RA-GEF exhibited not only a GTP-dependent binding activity to Rap1A at its RA **domain** but also an activity to stimulate GDP/GTP exchange of Rap1A both in vitro and in vivo at the segment containing its REM and GEF **domains**. However, it did not exhibit any binding or GEF activity toward Ras. On the other hand, Ce-RA-GEF associated with and stimulated GDP/GTP exchange of both Ras and Rap1A. These results indicate that Ce-RA-GEF and Hs-RA-GEF define a novel class of Rap1A GEF mols., which are conserved through evolution.

IT G proteins (guanine nucleotide-binding proteins)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(smg-21 (**small-mol.**-weight, 21,000-mol.-weight), Rap1A; sequence of RA-GEF of C. elegans, novel Rap1A guanine nucleotide exchange factor containing Ras/Rap1A-associating domain, and its conservation between nematode and humans)

=> s guy r?/au;s kuast i?/au;s harasco j?/au
L42 418 FILE MEDLINE
L43 653 FILE BIOSIS

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

```
L44         469 FILE EMBASE
L45         667 FILE CAPLUS

TOTAL FOR ALL FILES
L46        2207 GUY R?/AU


L47           0 FILE MEDLINE
L48           0 FILE BIOSIS
L49           0 FILE EMBASE
L50           0 FILE CAPLUS

TOTAL FOR ALL FILES
L51           0 KUAST I?/AU


L52           0 FILE MEDLINE
L53           0 FILE BIOSIS
L54           0 FILE EMBASE
L55           0 FILE CAPLUS

TOTAL FOR ALL FILES
L56           0 HARASCO J?/AU

=> s fujii n?/au
L57         791 FILE MEDLINE
L58         971 FILE BIOSIS
L59         731 FILE EMBASE
L60        1911 FILE CAPLUS

TOTAL FOR ALL FILES
L61        4404 FUJII N?/AU

=> s l46 and l61
L62           5 FILE MEDLINE
L63           8 FILE BIOSIS
L64           5 FILE EMBASE
L65           7 FILE CAPLUS

TOTAL FOR ALL FILES
L66          25 L46 AND L61

=> dup rem l66
PROCESSING COMPLETED FOR L66
L67           10 DUP REM L66 (15 DUPLICATES REMOVED)

=> d 1-10

L67  ANSWER 1 OF 10     MEDLINE on STN                  DUPLICATE 1
AN   2004608183     MEDLINE
DN   PubMed ID: 15582423
TI   Discovery of potent thiosemicarbazone inhibitors of rhodesain and cruzain.
AU   Fujii Naoaki; Mallari Jeremy P; Hansell Elizabeth J; Mackey Z;
     Doyle Patricia; Zhou Y M; Gut Jiri; Rosenthal Philip J; McKerrow James H;
     Guy R Kiplin
CS   Department of Pharmaceutical Chemistry, University of California-San
     Francisco, San Francisco, CA 94143, USA.
SO   Bioorganic & medicinal chemistry letters, (2005 Jan 3) 15 (1) 121-3.
     Journal code: 9107377. ISSN: 0960-894X.
CY   England: United Kingdom
```

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200505
ED Entered STN: 20041208
Last Updated on STN: 20050503
Entered Medline: 20050502

L67 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:905878 CAPLUS
DN 141:379805
TI A preparation of indole derivatives, useful as PDZ-domain inhibitors
IN **Guy, Rodney Kiplin**; Kuntz, Irwin D.; Haresco, Jose; **Fujii, Naoaki**; Novak, Kathleen P.; Stokoe, David; He, Biao; You, Liang; Xu, Zhidong; Jablons, David M.
PA The Regents of the University of California, USA
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004092346	A2	20041028	WO 2004-US11619	20040415
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005043385	A1	20050224	US 2004-826175	20040415
PRAI US 2003-463198P	P	20030415		

OS MARPAT 141:379805

L67 ANSWER 3 OF 10 MEDLINE on STN DUPLICATE 2
AN 2004002110 MEDLINE
DN PubMed ID: 14698174
TI A novel protein crosslinking reagent for the determination of moderate resolution protein structures by mass spectrometry (MS3-D).
AU **Fujii Naoaki**; Jacobsen Richard B; Wood Nichole L; Schoeniger Joseph S; **Guy R Kiplin**
CS Department of Pharmaceutical Chemistry, University of California at San Francisco, San Francisco, CA 94143, USA.
SO Bioorganic & medicinal chemistry letters, (2004 Jan 19) 14 (2) 427-9.
Journal code: 9107377. ISSN: 0960-894X.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200409
ED Entered STN: 20040106
Last Updated on STN: 20040922
Entered Medline: 20040921

L67 ANSWER 4 OF 10 MEDLINE on STN DUPLICATE 3

AN 2003507532 MEDLINE
DN PubMed ID: 14518976
TI A selective irreversible inhibitor targeting a PDZ protein interaction domain.
AU **Fujii Naoaki**; Haresco Jose J; Novak Kathleen A P; Stokoe David; Kuntz Irwin D; **Guy R Kiplin**
CS Department of Pharmaceutical Chemistry, University of California at San Francisco, Genentech Hall, Mission Bay, 600 16th Street 2280, San Francisco, California 94143-2280, USA.
NC GM31497 (NIGMS)
GM56531 (NIGMS)
SO Journal of the American Chemical Society, (2003 Oct 8) 125 (40) 12074-5.
Journal code: 7503056. ISSN: 0002-7863.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200401
ED Entered STN: 20031031
Last Updated on STN: 20040121
Entered Medline: 20040120

L67 ANSWER 5 OF 10 MEDLINE on STN DUPLICATE 4
AN 2003115074 MEDLINE
DN PubMed ID: 12627945
TI Role of electrostatic interactions in PDZ domain ligand recognition.
AU Harris Baruch Z; Lau Francis W; **Fujii Naoaki**; **Guy R Kiplin**; Lim Wendell A
CS Program in Biological Sciences, Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California 94143, USA.
SO Biochemistry, (2003 Mar 18) 42 (10) 2797-805.
Journal code: 0370623. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 20030312
Last Updated on STN: 20030702
Entered Medline: 20030701

L67 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:184277 CAPLUS
TI Targeting PDZ-domain by rationally designed nonpeptide small molecules: Structure and irreversibility
AU **Fujii, Naoaki**; Haresco, Jose J.; Novak, Kathleen A. P.; Stokoe, David; Kuntz, Irwin D.; **Guy, R. Kip**
CS Department of Pharmaceutical Chemistry, University of California, San Francisco, CA, 94143-0446, USA
SO Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-311 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69DSA4
DT Conference; Meeting Abstract
LA English

L67 ANSWER 7 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:411534 BIOSIS
DN PREV200300411534

TI Targeting PDZ-domain by rationally designed non-peptide small molecules: Structure and irreversibility.
AU **Fujii, Naoaki** [Reprint Author]; Haresco, Jose J.; Novak, Kathleen A. P. [Reprint Author]; Stokoe, David; Kuntz, Irwin D.; **Guy, R. Kip**
CS Department of Pharmaceutical Chemistry, University of California, San Francisco, 513 Parnassus Ave, San Francisco, CA, 94143-0446, USA nkfj@itsa.ucsf.edu
SO Abstracts of Papers American Chemical Society, (2003) Vol. 225, No. 1-2, pp. MEDI 311. print.
Meeting Info.: 225th American Chemical Society (ACS) National Meeting. New Orleans, LA, USA. March 23-27, 2003. American Chemical Society.
ISSN: 0065-7727 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 10 Sep 2003
Last Updated on STN: 10 Sep 2003

L67 ANSWER 8 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:402097 BIOSIS
DN PREV200300402097
TI Design, synthesis, and investigation of inhibitors of the function of PDZ domains.
AU Novak, Kathleen Pendola [Reprint Author]; **Fujii, Naoaki**; Stokoe, David; **Guy, R. Kip**
CS Pharmaceutical Chemistry, University of California San Francisco, 513 Parnassus Ave, San Francisco, CA, 94143, USA
kpendol@itsa.ucsf.edu; nkfj@itsa.ucsf.edu; dstokoe@cc.ucsf.edu; rguy@cgl.ucsf.edu
SO FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 844.15. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.
ISSN: 0892-6638 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Sep 2003
Last Updated on STN: 3 Sep 2003

L67 ANSWER 9 OF 10 MEDLINE on STN DUPLICATE 5
AN 2002406486 MEDLINE
DN PubMed ID: 12161160
TI Investigation of the PDZ domain ligand binding site using chemically modified peptides.
AU Novak Kathleen A P; **Fujii Naoaki**; **Guy R Kiplin**
CS Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94143-0446, USA.
SO Bioorganic & medicinal chemistry letters, (2002 Sep 2) 12 (17) 2471-4.
Journal code: 9107377. ISSN: 0960-894X.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 20020806
Last Updated on STN: 20030801
Entered Medline: 20030731

L67 ANSWER 10 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:166926 BIOSIS
DN PREV200300166926
TI Targeting PDZ-domain by novel non-peptide small molecules -design and evaluation, structure and irreversibility.
AU **Fujii, N.** [Reprint Author]; Haresco, J. J.; Novak, K. A. [Reprint Author]; Kuntz, I. D.; **Guy, R. K.** [Reprint Author]
CS Department of Pharmaceutical Chemistry, UC-San Francisco, San Francisco, CA, USA
SO Molecular Biology of the Cell, (Nov 2002) Vol. 13, No. Supplement, pp. 360a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology. San Francisco, CA, USA. December 14-18, 2002. American Society for Cell Biology.
ISSN: 1059-1524 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 2 Apr 2003
Last Updated on STN: 2 Apr 2003

=> s (l46 or l61) and l20
L68 4 FILE MEDLINE
L69 7 FILE BIOSIS
L70 4 FILE EMBASE
L71 6 FILE CAPLUS

TOTAL FOR ALL FILES
L72 21 (L46 OR L61) AND L20

=> s l72 not (l40 or l66 or l30)
L73 1 FILE MEDLINE
L74 1 FILE BIOSIS
L75 1 FILE EMBASE
L76 1 FILE CAPLUS

TOTAL FOR ALL FILES
L77 4 L72 NOT (L40 OR L66 OR L30)

=> dup rem l77
PROCESSING COMPLETED FOR L77
L78 1 DUP REM L77 (3 DUPLICATES REMOVED)

=> d ibib abs

L78 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 1998058950 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9395497
TITLE: MAGI-1, a membrane-associated guanylate kinase with a unique arrangement of protein-protein interaction domains.
AUTHOR: Dobrosotskaya I; **Guy R K**; James G L
CORPORATE SOURCE: Department of Biochemistry, The University of Texas Health Science Center, San Antonio, Texas 78284-7760, USA.
CONTRACT NUMBER: HL20948 (NHLBI)
SOURCE: Journal of biological chemistry, (1997 Dec 12) 272 (50) 31589-97.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF027503; GENBANK-AF027504; GENBANK-AF027505
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980115

AB Membrane-associated guanylate kinase (MAGUK) proteins participate in the assembly of multiprotein complexes on the inner surface of the plasma membrane at regions of cell-cell contact. MAGUKs are characterized by three types of protein-protein interaction modules: the **PDZ domain**, the Src homology 3 (SH3) **domain**, and the guanylate kinase (GuK) **domain**. The arrangement of these **domains** is conserved in all previously known MAGUKs: either one or three **PDZ domains** in the NH2-terminal half, followed by the SH3 **domain**, followed by a COOH-terminal GuK **domain**. In this report, we describe the cDNA cloning and subcellular distribution of MAGI-1, a MAGUK with three unique structural features: 1) the GuK **domain** is at the NH2 terminus, 2) the SH3 **domain** is replaced by two WW **domains**, and 3) it contains five **PDZ domains**. MAGI-1 mRNA was detected in several adult mouse tissues. Sequence analysis of overlapping cDNAs revealed the existence of three splice variants that are predicted to encode MAGI-1 proteins with different COOH termini. The longest variant, MAGI-1c, contains three bipartite nuclear localization signals in its unique COOH-terminal sequence and was found predominantly in the nucleus of Madin-Darby canine kidney cells. A shorter form lacking these signals was found primarily in membrane and cytoplasmic fractions. This distribution, which is reminiscent of that seen for the tight junction protein ZO-1, suggests that MAGI-1 may participate in the transmission of regulatory signals from the cell surface to the nucleus.

=> dis his

(FILE 'HOME' ENTERED AT 15:43:05 ON 21 DEC 2005)

FILE 'REGISTRY' ENTERED AT 15:43:16 ON 21 DEC 2005
L1 STR
E TETRAZOLYL/CN
L2 1 S E3
E "5-TETRAZOLYL"/CN 5
E TETRAZOLE/CN 5
L3 1 S E3
L4 STR L1
L5 0 S L4
L6 0 S L4 FUL
L7 STR L4
L8 0 S L7
L9 2 S L7 FUL

FILE 'CAPLUS' ENTERED AT 15:57:42 ON 21 DEC 2005
L10 1 S L9

FILE 'REGISTRY' ENTERED AT 15:58:03 ON 21 DEC 2005
L11 STR
L12 1 S L11
L13 9 S L11 FUL

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     FILE 'CAPLUS' ENTERED AT 16:03:25 ON 21 DEC 2005
L14           8 S L13

     FILE 'REGISTRY' ENTERED AT 16:03:40 ON 21 DEC 2005
                 E PDZ/CN 5
L15          71 S PDZ ?/CN

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L16        1396 FILE MEDLINE
L17        1845 FILE BIOSIS
L18        1286 FILE EMBASE
L19        1824 FILE CAPLUS
     TOTAL FOR ALL FILES
L20        6351 S L15 OR PDZ(L)DOMAIN
L21         264 FILE MEDLINE
L22         272 FILE BIOSIS
L23         242 FILE EMBASE
L24         362 FILE CAPLUS
     TOTAL FOR ALL FILES
L25        1140 S L20 AND INHIBIT?
L26           0 FILE MEDLINE
L27           0 FILE BIOSIS
L28           0 FILE EMBASE
L29           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L30           3 S COMBINAT? LIBRARY AND L25
L31         162 FILE MEDLINE
L32         239 FILE BIOSIS
L33         152 FILE EMBASE
L34         284 FILE CAPLUS
     TOTAL FOR ALL FILES
L35         837 S L20 AND SCREEN?
L36           0 FILE MEDLINE
L37           1 FILE BIOSIS
L38           0 FILE EMBASE
L39           6 FILE CAPLUS
     TOTAL FOR ALL FILES
L40           7 S SMALL MOLECULE AND (L35 OR L25)
L41           7 DUP REM L40 (0 DUPLICATES REMOVED)
L42         418 FILE MEDLINE
L43         653 FILE BIOSIS
L44         469 FILE EMBASE
L45         667 FILE CAPLUS
     TOTAL FOR ALL FILES
L46        2207 S GUY R?/AU
L47           0 FILE MEDLINE
L48           0 FILE BIOSIS
L49           0 FILE EMBASE
L50           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L51           0 S KUAST I?/AU
L52           0 FILE MEDLINE
L53           0 FILE BIOSIS
L54           0 FILE EMBASE
L55           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L56           0 S HARASCO J?/AU
L57         791 FILE MEDLINE
L58         971 FILE BIOSIS
L59         731 FILE EMBASE
```

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

```
L60          1911 FILE CAPLUS
     TOTAL FOR ALL FILES
L61          4404 S FUJII N?/AU
L62             5 FILE MEDLINE
L63             8 FILE BIOSIS
L64             5 FILE EMBASE
L65             7 FILE CAPLUS
     TOTAL FOR ALL FILES
L66            25 S L46 AND L61
L67            10 DUP REM L66 (15 DUPLICATES REMOVED)
L68             4 FILE MEDLINE
L69             7 FILE BIOSIS
L70             4 FILE EMBASE
L71             6 FILE CAPLUS
     TOTAL FOR ALL FILES
L72            21 S (L46 OR L61) AND L20
L73             1 FILE MEDLINE
L74             1 FILE BIOSIS
L75             1 FILE EMBASE
L76             1 FILE CAPLUS
     TOTAL FOR ALL FILES
L77             4 S L72 NOT (L40 OR L66 OR L30)
L78             1 DUP REM L77 (3 DUPLICATES REMOVED)

=> d l6 que stat;d l9 que stat;d l13 que stat
L4               STR
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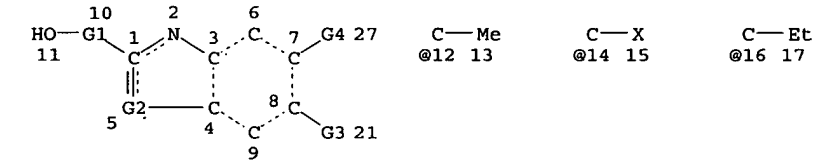

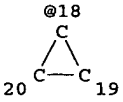

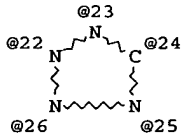


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VAR G3=ME/ET/I-PR/N-PR/18/X/O/S
VAR G4=23/24/25/22/26
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
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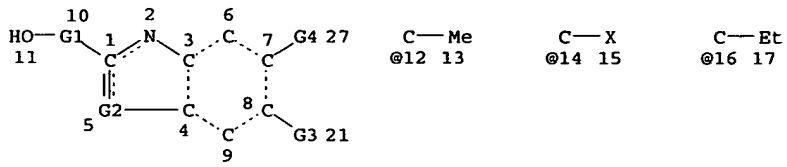
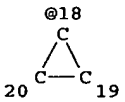
L7 STR



C—Me
@12 13

C—X
@14 15

C—Et
@16 17



O~C~O
28 @29 30

O~C~N
31 @32 33

O~C~N~S~O
34 @35 36 37 38

CH2·CO2H
@39 40

C~OH
@41 42

CH2·C~N
@43 44 45

REP G1=(1-4) C
VAR G2=CH/14/12/16
VAR G3=ME/ET/I-PR/N-PR/18/X/O/S
VAR G4=CO2H/29/32/35/39/41/43
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

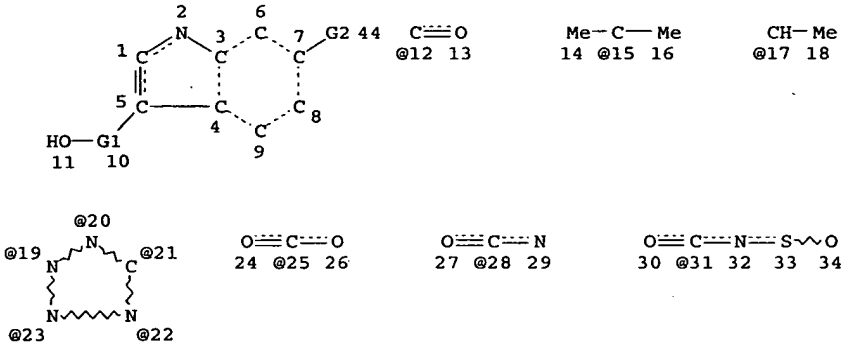
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 41

STEREO ATTRIBUTES: NONE
L9 2 SEA FILE=REGISTRY SSS FUL L7

100.0% PROCESSED 14142 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

L11 STR

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86



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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 44

STEREO ATTRIBUTES: NONE
L13 9 SEA FILE=REGISTRY SSS FUL L11

100.0% PROCESSED 26897 ITERATIONS 9 ANSWERS
SEARCH TIME: 00.00.01

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	69.44	629.81
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-6.57	-13.14

STN INTERNATIONAL LOGOFF AT 16:08:24 ON 21 DEC 2005